1.0 SCIENTIFIC ABSTRACT

An estimated 42,000 people develop head and neck cancer annually in the U.S. The treatment options available to these people are limited to surgery, radiotherapy and/or chemotherapy which are toxic as well as functionally and cosmetically debilitating. The five-year survival in advanced head and neck squamous cell carcinoma (HNSCC) is less than 30%. Since recurrent head and neck squamous cell carcinoma patients have low survival and salvage rates, a newer modality of therapy is desirable for these patients. One potential modality is E1A gene therapy.

The E1A protein functions as a tumor inhibitor gene via multiple pathways when transfected in cancer cells: (i) by virtue of its ability to modulate transcription, E1A downregulates the HER-2/*neu* p185 oncoprotein and matrix metalloproteases. The overexpression of the HER-2/*neu* oncogene is associated with enhanced metastatic potential, drug resistance and poor survival. E1A mediated downregulation of HER-2/*neu* and matrix metalloproteases results in the loss of the malignant and metastatic phenotype; (ii) by interacting with cellular proteins, E1A induces apoptosis through the p53 or alternate apoptotic pathways; and (iii) via immunodominant epitopes, E1A elicits an immune response making cells expressing E1A susceptible to lysis by non-specific (NK cells) and specific (CTLs) immune cells.

E1A-mediated inhibition of tumor growth and progression was demonstrated in three distinct xenotropic animal models. Treatment with E1A Lipid Complex, resulted in tumor growth inhibition and extended survival of *nu/nu* mice bearing either the SKOV-3 human ovarian, MDA-MB435 human breast (both lines overexpress HER-2/*neu*) or WSUHN-31 human HNSCC cancer cells (expresses basal level of HER-2/*neu*). The E1A Lipid Complex consists of the E1A plasmid complexed to the cationic lipid gene delivery system comprised of DC-Cholesterol* and DOPE**. In a phase I study of patients with unresectable, recurrent head and neck cancer and metastatic breast cancer treated with E1A Lipid Complex, there were no dose-related toxicities. Eight of eighteen patients enrolled in the Phase 1 study completed the full course of 10 injections and 12 week follow-up. Of these eight patients, three patients had disease progression, four had stable disease and one had a minor response in the treated tumor.

In this Phase II trial the E1A Lipid Complex will be administered to 40 evaluable patients with unresectable head and neck tumors. An interim analysis will be performed after treatment of 20 evaluable patients. If at least one complete or partial response is observed in this cohort of patients, an additional 20 patients may be enrolled. Tumors will be injected at a single dose of 30 μg DNA/cm^3 tumor, according to a dose schedule of 3 daily doses followed by weekly doses through day 50. The major endpoints of this trial are safety and evaluation of tumor response by assessments of two-dimensional cross-products from CT scans performed at baseline and week 12 or time of patient withdrawal. Additional measurements, including pain assessment and Quality of Life surveys, will be taken as outlined in clinical protocol.

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* 3β[N', N'-dimethylaminoethane)-carbamoyl] cholesterol
** 1,2-dioleoyl-sn-glycero-3-phosphatidylethanolamine